DEVICE FOR DELIVERY OF A LIQUID VEHICLE

THE CURRENT INVENTION

The present invention relates to improvements in the delivery of an active agent into an environment (whether *in vivo* or *in vitro*) and particularly, although not solely, to devices having application in the delivery of one or more active ingredients into a mammal (eg; intra ruminally or intra vaginally) or into an aqueous environment, e.g. an aquarium.

SUMMARY OF THE INVENTION

In our PCT/NZ98/00011 we disclose in some detail the background to the passive and active release of active ingredient(s) into the body cavity of mammals including the vaginal tract and the rumen. PCT/NZ96/00024 (WO 96/29025) discloses a microprocessor controlled active release device for intra vaginal insertion with its retention being dependent on variable geometries possible using deployment members of a kind as disclosed in NZ Patent Specifications 193976 and 200564.

A problem discussed in such specification is the release profile of a substance delivery device whether for a body cavity or otherwise (for example, a liquid body such as an aquarium) arising from a passive leakage of material which can affect the overall release profile.

We have investigated different known procedures of active release and have considered new procedures insofar as the means of expression of a liquid vehicle from a reservoir of reducible volume is concerned. It is to such substance delivery devices and their use that the present invention is directed.

In a first aspect the present invention consists in a **(preferably body cavity) liquid delivery device** comprising or including

a housing defining a barrel with an outlet,

a piston disposed in said barrel and moveable to reduce the available volume for liquid between said piston and said outlet,

a liquid within said barrel between said outlet and said piston, and

a battery powered electrical circuit disposed in said housing capable of being

energised to generate gas or gases confined within said housing yet capable of moving said piston along said barrel thereby to express liquid out through said outlet.

Preferably the battery itself of said electrical circuit emits said gas or gases upon energisation of the electrical circuit by said battery.

In another form said electrical circuit defines an electrolysis cell with a hydrogel or electrolyte and the gas issues or gases issue from said hydrogel or electrolyte.

Preferably the battery powered electrical circuit includes a battery of a kind as disclosed in US Patent 5,242,565.

Preferably said battery powered electrical circuit, where an electrolysis cell is involved, includes an electrolysis cell of a kind as disclosed in US Patent 5,352,464.

Preferably said electrical circuit provides a continuous rate of gas production by the action of a continuous current to the electrolysis cell or gas emitting battery.

Alternatively said electrical circuit provides a discontinuous rate of gas production by the action of a discontinuous current, for example, as might be provided by a microprocessor, to the electrolysis cell or gas emitting battery.

Preferably where said battery powered electrical circuit provides a continuous rate of gas production, such production is dependent upon at least one of the group consisting of

(a) a selected resistor in series,

(b) a selected variable resistor and a setting of a desired resistance in series, and

(c) a selected microprocessor to control the current.

Preferably the battery powered electrical circuit is one having a known or calibrated profile of gas generation that will lead to a related profile of liquid release from said outlet.

Preferably said device is an intra vaginal device .

Preferably said housing has associated therewith at least one deployable retention member to enable the retention of the device in the vagina after insertion in the vagina of a target mammal whilst said at least one retention member is not deployed.

Preferably said at least one retention member comprises at least two wings which resiliently deploy once inserted and preferably are no longer restrained by an insertion

tool.

Preferably the retention feature(s) is (are) those typified in the disclosure of PCT/NZ97/00052, PCT/NZ98/00011 and PCT/NZ98/00024 (and any specification referred to therein), the full content of which is hereby here incorporated by way of reference.

Preferably said liquid includes progesterone in an appropriate liquid carrier.

In another embodiment said device is an intra ruminal device.

Preferably said intra ruminal device is retainable in the rumen of a target mammal by means of its density (at least up until the depletion of the liquid from said housing) or by deployment of at least one retention member.

Preferably said liquid includes at least one or more of water, ethanol and benzyl alcohol.

Preferably said battery powered electrical circuit includes a switch capable of being actuated immediately or after a delay to commence the generation of a gas or gases.

Preferably said outlet is provided with a closure capable of being removed or ruptured or dissolved in body fluids.

Preferably said closure is capable of being removed or ruptured under the pressurisation of the liquid within said housing upon energisation of the battery powered electrical circuit.

Preferably said liquid is of a volume of from 5 to 100 mL and said piston is movable within said housing to express substantially all of such liquid from the housing.

Preferably said device is insertable, retainable and removal from the vaginal tract of a target species mammal, there being a conduit or passageway disposed to allow pressure equalisation outside of the device at the innermost and outmost extent of the device in the vaginal tract.

Preferably said device is substantially as hereinafter described with reference to the accompanying drawings.

In still another aspect the invention consists in an intra vaginal delivery device comprising or including

a housing defining a barrel with an outlet,

variable geometry vaginal retention means carried by said housing,

a piston disposed in said barrel and moveable to reduce the available volume for liquid between said piston and said outlet,

a progesterone carrying liquid within said barrel between said outlet and said piston, and

a battery powered electrical circuit disposed in said housing capable of being energised to generate gas or gases from the battery of said battery powered electrical circuit, such generated gas or gases being confined within said housing and being capable of moving said piston along said barrel thereby to express liquid out through said outlet

and wherein said battery powered electrical circuit provides a discontinuous or continuous gas production upon initiation of energisation with rate and/or timing dependent upon at least one of the group consisting of

(a) a selected resistor in series,

(b) a selected variable resistor and a setting of a desired resistance in series, and

(c) a selected microprocessor to control the current.

In still a further aspect the present invention consists in an intra vaginal delivery device comprising or including

an elongate housing defining a barrel with an outlet at one end (the "outlet end"),

a piston disposed in said barrel and moveable towards the outlet end to reduce the available volume for liquid between said piston and said outlet,

a progesterone including liquid within said barrel between said outlet and said piston, the volume of such liquid being from 5 to 100 mL,

wings dependent from said housing capable of self deployment from a vaginal tract insertion condition to assume a vaginal tract retention geometry for the target species mammal,

a battery powered electrical circuit disposed in said housing at the non outlet end region thereof capable of being initialised in order to energise the electrical circuit from the battery thereof, such battery generating once the electrical circuit is energised at least one gas confined within said housing, such gas being capable when in sufficient

quantities to move said piston along said barrel thereby to express said liquid out through said outlet.

In another aspect the invention consists in **a method of providing an active release of a liquid within a body cavity of a target species mammal** which comprises or includes locating in such a body cavity a device as claimed in any one of the preceding claims with said battery powered electrical circuit energised or committed to be energised.

In still another aspect the invention consists in **a method of delivering an active amount of a progesterone into the vaginal tract of a target species mammal** which comprises

locating a device of the present invention in such tract after initiation of the device, and

allowing the device to actively express the liquid from said housing under the effect, via said piston, of the gas or gases generated by the energised battery powered electrical circuit.

Preferably said method involves removing said device after a sufficient time of liquid delivery.

In another aspect the invention is a method when performed substantially as herein described with or without reference to any one or more of the accompanying drawings.

In still other aspects the present invention consists in a method of providing a delayed release of a liquid vehicle into a body cavity of a mammal or into a liquid environment or other environment which comprises the operative use of a delivery device in accordance with the present invention.

Preferably said devices do not include a dip tube or the equivalent of a kind as defined in, for example, PCT/NZ98/00011.

In still a further aspect the present invention consists in an intra ruminal device which is also a delivery device in accordance with the present invention.

In still a further aspect the present invention consists in an intra vaginal device which is also a delivery device in accordance with the present invention.

In still a further aspect the present invention consists in any of the devices or

apparatus previously defined whereby means is provided to enable for equalisation of pressures between the zone externally adjacent said outlet with some region of the device having a closer access to ambient condition when the device is retained in a body cavity, such means providing for fluid (preferably gas and preferably air) communication to minimise pressure differentials adjacent the outlet as a result of movement of walls of the body cavity and an air seal about the device in the body cavity.

Preferably the arrangement is of any kind typified by the diagrammatic form shown in, for example, Figure 5.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred forms of the present invention will now be described with reference to the accompanying drawings in which;

Figure 1A shows a balloon or membrane containing embodiment of a device,

Figure 1B is a piston including syringe-like embodiment,

Figure 2 is a plot for the Figure 1A and B embodiments of volume released against time,

Figure 3 compares for the Figures 1A device the *in vivo* and *in vitro* delivery profiles with a plot of volume release against time,

Figure 4 is a similar comparison for the Figure 1B device plotted in a similar fashion to that of Figure 3,

Figure 5 shows how (in this case for the more energy demanding but better *in vivo* delivery profile device - that of Figure 1B) the use of a tube whereby the transient pressure differentials (eg; in the vaginal tract) adjacent the outlet may be reduced,

Figure 6 is a plot of the plasma progesterone following intra vaginal insertion of a device of Figure 1A,

Figure 7 is a plot of the plasma progesterone following intra vaginal insertion of a device of Figure 1B with three different progesterone formulations,

Figures 8A through 8D show a simple circuit diagram each involving an electrolytic cell, **Figure 8A** shows an electrolytic cell in series with resistor and power source, **Figure 8B** shows an electrolytic cell in series with a variable resistor and power

source, **Figure 8C** shows an electrolytic cell controlled by powered microprocessor and **Figure 8D** shows an electrolytic cell controlled by powered microprocessor,

Figure 9A through 9D show a series of different circuits appropriate where a battery of a kind capable of generating a gas or gases is utilised in the circuit, **Figure 9A** showing a gas cell of the type described by US Patent 5,242,565 in series with a resistor, **Figure 9B** shows a gas cell of the type described by US Patent 5,242,565 in series with a variable resistor, **Figure 9C** shows a gas cell of the type described by US Patent 5,242,565 controlled by a gas cell of the type described by US Patent 5,242,565 powered microprocessor and **Figure 9D** shows a gas cell of the type described by US Patent 5,242,565 controlled by a microprocessor powered by an external power source, and

Figure 10A shows in broken outline two insertion conditions for self deployable wings and **Figure 10B** shows such wings deployed to a vaginal tract retention condition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention recognises advantages that might flow to particularly body cavity retainable devices (eg; intra vaginal or intra ruminal devices) where a liquid vehicle is to be actively released and there is a desire to reduce the ratio of passive release to active release. In this respect embodiments to be discussed hereinafter recognise advantages that arise from the use of gas generation for the purposes of reducing the available volume in a reservoir for the liquid vehicle to be expressed.

For low energy usage preferably an inflatable device as hereinafter described by reference to Figure 1 is preferred yet surprisingly as will hereinafter be described we have determined that a plunger or piston like reservoir reduction provides a better *in vivo* release profile over that of the inflation option owing to a reduction in passive delivery. Where therefore rapid release with some passive content is not of concern significant energy savings are available for an active release device utilising the inflation option. Where however controlled release is of primary importance and/or there is no concern with an initial startup delay or a startup delay is desired the option hereinafter described by reference to Figure 1B with the use of a gas generated battery

is to be preferred even though it will be a higher energy requirement for such an option.

The devices of Figures 1A and 1B utilize electronically controlled gas to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US5352464) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The device of Figure 1A incorporates a balloon that upon the production of gas and its movement into the balloon means the balloon expands to fill the reservoir containing the liquid vehicle. This expansion results in the delivery of the liquid vehicle out of the outlet.

The device of Figure 1B incorporates a piston that upon the production of gas behind the piston results in its migration towards the outlet. This forward migration results in the delivery of the liquid vehicle.

In Figure 1A the balloon 1 is disposed within a syringe like reservoir 2 having an outlet 3. The liquid vehicle 4 is interposed between the walls of the reservoir 2 the outlet 3 and the balloon 1 so that inflation thereof will have the effect of expressing the liquid vehicle 4 out of the outlet 3. The inflation is by means of electronic gas production at 5 which feeds gas via an appropriate conduit 6 to the confines of the balloon or diaphragm 1. Such conduit is indicated as 6.

The arrangement as in Figure 1B is much the same save that instead of the balloon or membrane 1, a piston 7 is provided which will move to reduce the volume for the liquid vehicle 4 therebetween and the outlet 3.

In use when both devices of Figures 1A and 1B are operated with the same rate of gas production the arrangement as shown in Figure 1A with the inflatable balloon allows for a more rapid onset of delivery with a greater flow of vehicle compared to the piston arrangement which is characterised by a lag in the onset of delivery and a reduced delivery rate.

Accordingly for some applications the device of Figure 1 offers advantages over a device of Figure 1B. In the plot of Figure 2, the lag in the onset of delivery from the configuration of Figure 1B is readily apparent from the lower line on the graph,

Preferably the control circuitry involves a resistor (variable or otherwise) of an appropriate kind to affect the current flow. The circuitry may optionally be

microprocessor controlled.

The liquid vehicle is preferably at least primarily aqueous, organic or non-organic as far as its liquid content is concerned. Whilst in preferred forms the vehicle as a whole may be viewed overall as a liquid it need not necessarily be a solution. The liquid itself may be the active or merely a liquid carrier for the active elsewhere in the vehicle.

Accordingly, the term "liquid vehicle" or "liquid" should be interpreted as including any one or more of a suspension, a dispersion, an emulsion, a susproemulsion, a solution and the like, and preferably a progesterone including "liquid".

Whilst the arrangement of Figure 1A has definite efficiencies in respect of the energisation required for the purpose of gas generation per volume of liquid vehicle dispensed and the lack of delay in such dispensation, the device of a kind shown in Figure 1B has been found to improve the delivery of liquid vehicle whilst inserted into a body cavity such as the rumen or the vaginal cavity.

Figure 3 shows a plot of liquid vehicle delivered in grams against time and days with a device as depicted in Figure 1A. The straighter line is the *in vitro* delivery of vehicle from a device of Figure 1A whilst the more curved line represents the *in vivo* delivery profile for an identical device. It is therefore surprising that whilst a device as shown in Figure 1A has the comparative *in vitro/in vivo* profiles shown in Figure 3, that a device as shown in Figure 1B has more agreement between the *in vitro/in vivo* profiles. In this respect see Figure 4 where in a similar way to that of Figure 3 the comparative performance of a device as in Figure 1B is shown in the *in vitro* and *in vivo* delivery modes. That line indicated with the shaded squares represents the *in vivo* profile.

For the purpose of the generation of the data shown in Figures 3 and 4 the volume of liquid vehicle being dispensed was in each case water to be expressed out of a 2 mm diameter outlet. In each case the syringe like reservoir was of a cylindrical form and was powered over the duration of the comparative trials by a galvanic cell of the kind disclosed in US Patent 5242565 capable of generating over the life of the cell to depletion up to 180 ml of hydrogen when measured at normal atmospheric conditions at sea level.

Figure 5 shows a variation of the device as shown in Figure 1A. In this form means is provided to reduce variations at least over the medium term in the pressure differential in a body cavity with that of the ambient atmosphere. For this purpose a tube 8 is provided which, in the case of an intra vaginal device as shown in Figure 5 (the variable geometry wings not being shown for convenience, but do see our PCT/NZ97/00052 (published as WO97/40776)) tends to equilibralise pressure externally of the device in a vaginal tract. Indeed the tube 8 if flexible may serve in part as a withdrawal mechanism for the device and as a passageway 9 through to an outlet zone 10. Experimentation with, for example, cattle has shown in the short to medium terms significant fluctuations in the pressure about the outlet of devices of the kind shown in Figures 1A and 1B which have the effect of providing a different net force acting on the liquid vehicle yet to be expressed. This is particularly disadvantageous with the device of Figure 1A where there is (as demonstrated in Figure 2) a more rapid onset of delivery following any adjustment in pressure on the liquid vehicle.

Accordingly, the device of Figure 1B has a better profile under variations of vaginal tract pressure without any arrangement that seeks to reduce localised pressure variations externally of the device.

Description of the technology:

The devices depicted in Figures 1A and 1B utilize electronically controlled gas 5 to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US 5354264) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The top device of Figure 1A incorporates a balloon that upon the production of gas within 6 the balloon 1 expands to fill the reservoir 2 containing a vehicle 4. This expansion results in the delivery of the liquid vehicle out of the outlet 3.

The bottom device of Figure 1B incorporates a piston 7 that upon the production of gas behind 6 the piston results in its migration towards the outlet. This forward migration results in the delivery of vehicle.

Figure 3 shows both the in vitro and in vivo delivery of vehicle from a body cavity for the device of Figure 1A.

Figure 4 shows the in vitro and in vivo agreement of vehicle delivered for the device of Figure 1B.

The device of Figure 5 utilizes electronically controlled gas to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US 5354264) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The device of Figure 5 shows improvements to enable a more controlled delivery of vehicle to a body cavity. The addition of a tube 9 (or indeed any passageway from one end to the other) facilitates the maintenance of a constant pressure within the cavity 10 in relation to the exterior pressure 8.

Example 1:

Formulation: Progesterone 15 mg/ml dissolved in ethanol.

Device: As shown in Figure 1A

Comment: Delivery profile characterised by a dose dump soon after insertion, followed by a reduction in plasma progesterone delivery on day due to the dose dump. See Figure 6. Figure 6 shows a plot of plasma progesterone concentration following the intra vaginal insertion of a device as per Figure 1A. Error bars are standard error means.

Example 2:

Formulation 1: Progesterone 15 mg/ml dissolved in ethanol.

Formulation 2: Progesterone 15 mg/ml suspended in water.

Formulation 3: Progesterone 15 mg/ml dissolved in hydroxypropyl b-cyclodextrin (20%w/v) solution.

Device: As shown in Figure 1B.

Comment: Delivery profile characterised by a rapid rise to desired levels soon after insertion, followed by a controlled delivery of progesterone over the remained of the insertion period. See Figure 7. Figure 7 shows a plot of the plasma progesterone concentration following the intra vaginal insertion of a device as per Figure 1B containing 1 of 3 formulations; alcoholic solution (diamond symbol), aqueous

suspension (triangle symbol with broken line) or aqueous cyclodextrin (square symbol). Error bars are standard error means.

Figures 8A to 8D and Figures 9A to 9D describe options available for circuits where respectively (Figures 8A to 8D) and electrolytic cell and (Figures 9A to 9D) a battery or gas cell of the type described by US Patent 5,242,565 is used. Appropriate electrolytic cell is that using, for example, a hydrogel as disclosed in US Patent 5,354,264.

The present invention as can be seen from the disclosure and the drawings (including those of the prior art referenced earlier in respect of vaginal tract retention features) can be used to deliver progesterone requirements prior to active withdrawal to allow the onset of oestrus. Again reference is drawn to such art as to insertion, retention options and withdrawal facilitating options.